PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Staley A. Brod	Group Art Unit: 1647
Serial No.: 08/844,731	Examiner: Jegatheesan Seharaseyon
Filed: April 21, 1997	Atty. Dkt. No.: CLFR:114US
For: METHODS OF TREATING AUTOIMMUNE DISEASES USING TYPE ONE INTERFERONS	

CERTIFICATE OF ELECTRONIC SUBMISSION

September 11, 2006

REPLY BRIEF

Sir:

Appellant hereby submits this Reply Brief in accordance with 37 C.F.R. §41.41, in response to the Examiner's Answer dated July 12, 2006, making the due date September 12, 2006. It is believed no other fees are required, however, if Applicant is mistaken, the Commissioner is authorized to withdraw any such fees from Fulbright & Jaworski L.L.P. Deposit Account No. 50-1212/CLFR:114US.

I. STATUS OF THE CLAIMS

Claims 1-7, 10, 12-15, 18 and 21-22 were previously canceled and thus claims 8-9, 11, 16-17, and 19-20 are currently pending in the case. The final rejection of claims 8-9, 11, 16-17 and 19-20 is the subject of the instant appeal.

II. GROUNDS OF THE REJECTION

Claims 8, 9, 11, 16, 17, 19 and 20 have been rejected under 35 U.S.C. 103(a) as unpatentable over Sobel, U.S. Patent No: 5,780,021 (hereafter "Sobel") in view of Cummins, Jr., U.S. Patent No: 5,019,382 (here after "Cummins '382") and further in view of Cummins, Jr., U.S. Patent No: 4,462,985 (hereafter "Cummins '985").

III. GROUNDS OF THE REJECTION

Claims 8, 9, 11, 16, 17, 19 and 20 have been rejected under 35 U.S.C. 103(a) as unpatentable over Sobel, U.S. Patent No: 5,780,021 (hereafter "Sobel") in view of Cummins, Jr., U.S. Patent No: 5,019,382 (here after "Cummins '382") and further in view of Cummins, Jr., U.S. Patent No: 4,462,985 (hereafter "Cummins '985").

IV. ARGUMENT

The rejection set forth by the Examiner alleges that the claimed method for treating or preventing IDDM comprising oral administration of 10,000 to 30,000 units of interferon alpha would have been obvious over Sobel in view of Cummins '985 and Cummins '382 at the time the invention was made. We would stress that the present invention is directed to the discovery of a critical dosing range for ***oral*** administration of interferon for IDDM. We submit that this critical range is the only range found by the Appellants where interferon appears to be ***orally*** active to suppress immune cell function in humans. We would point out that none of the references relied upon by the Examiner show actual working examples of **oral** administration of interferon for IDDM. Cummins '382 fails to mention IDDM, it actually teaches away from oral ingestion (swishing and gargling only) and it teaches away from the current dose range. Furthermore, in Sobel, oral administration is simply set forth in a laundry list of routes of administration, there is no data or examples of oral administration, and the dosage range actually taught by Sobel for IDDM is a much higher dose range that, as shown below, does not appear to be operable for oral administration. Finally, Cummins '985 which does concern oral administration of interferon in a range encompassing the claimed range teaches the use thereof for treating viral a neoplastic disease. However, treatment of such diseases involves activating the immune system rather than suppressing its function. Thus, Applicant maintains that the instant invention is not obvious in view of the cited references.

Applicant previously asserted that the Examiner has failed to make a *prima facie* showing of obviousness since the skilled artisan would neither be motivated to combine Sobel and Cummins '985 nor have a reasonable expectation of success in such a combination. In answer the arguments previously set forth by the Applicant, the Examiner has stated that individual references cited in an obviousness rejection can not be "attacked" individually. However, the

heart of Applicant's argument concerns whether the references are properly combinable and thus Applicant arguments are directed to the combination of the references as a whole. Briefly, Sobel teaches a dose range of interferon higher than the claimed range for the treatment insulin dependent diabetes mellitus (IDDM), demonstrating the efficacy of such dosing with injected interferon. Cummins '382 on the other hand, teaches a dose range *lower* than that claimed by Applicant for the treatment of autoimmune diseases. Finally, Cummins '985 teaches a dose range that encompasses Applicant's dose range however demonstrates the efficacy of this range in treating viral and neoplastic diseases. **None of these references, alone or in combination, render obvious the critical dose range of oral interferon claimed by the Applicant.**

The present invention is directed to the discovery of a critical dosing range for ***oral*** administration of interferon for IDDM. We submit that this critical range is the only range found by the Appellant where interferon appears to be ***orally*** active to suppress immune cell proliferation in humans. In particular, when administered to a human with autoimmune disease 10,000 or 30,000 units of interferon resulted in reduced peripheral blood mononuclear cell (PBMC) proliferation, a measure of immune cell activation see figure 12 and page 16 line 24 through page 16 line 2 of the specification). High doses such as 100,000 units however lacked this effect. These studies therefore demonstrate the that for oral administration a critical dose range (10,000 to 30,000 units/individual) is required therapeutic effect against immune cells.

Sobel teaches a method of treating IDDM with interferon but teaches dosage ranges that are higher than those of the subject claims while mentioning the possibility of oral administration only in passing. Sobel demonstrates the efficacy of interferon for treating IDDM using a intraperitoneal administration methods (see figures 1 and 2) and provides no teaching as to how a dose range may be modified for oral administration. Hence, to arrive at the effective, critical

dose range of oral interferon administration, as recited in the instant claims, a skilled artisan would be forced to turn to a secondary reference. Nonetheless, in the Examiner's Answer it is argued that Sobel suggests lower dose treatments stating that "less than 1 x 10^5 units, such as 5 x 10^4 units or lower [may be used]" (column 4, lines 15-16). However, even these lower doses are greater than those of the subject claims and the instant specification demonstrates that there is a significant functional difference between the doses suggested by Sobel and those of the instant claims. For example, when 1 x 10^5 units of interferon was administered to humans no reduction of peripheral blood mononuclear cell (PBMC) proliferation was exhibited where as an effect was seen with 10,000 and 30,00 unit doses (see figure 12 and page 16 line 24 through page 16 line 2 of the specification). Thus, it is argued that these studies show that 10,000 to 30,000 units of oral interferon constitutes a critical and nonobvious therapeutic range and represent a difference *in kind* between the dose range suggested by Sobel and that of the instant claims. *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955*)

Cummins '382 fails to mention IDDM, it actually teaches away from oral ingestion (swishing and gargling only) and it teaches away from the current dose range. The Examiner has suggested that a skilled artisan attempting to modify the protocol of Sobel for the purposes of oral administration might turn to the teaching of Cummins '382 which concerns the administration of low-dose interferon for treating autoimmune disease. However, though Cummins '382 concerns autoimmune diseases it does not mention treatment of IDDM and does not teach the oral (ingestion) of interferon rather it teaches contact between interferon and the oral mucosa, such as by swishing or gargling. The Examiner has correctly indicated that Cummins '382 teaches, in its broadest embodiment, a dose range of about 0.1 to about 5 **IU/lb** per day and that this dose range is equivalent to about 191.4 to about 9,570 **units** per individual

per day. However, this dose range does not, as alleged by the Examiner, encompass the dose range of the subject claims (10,000 to 30,000 units per individual). Quite to the contrary, Applicant reasserts that Cummins '382 teaches away from the dose range For example in column 4, lines 24- 32, Cummins '382 states:

> *Treatment of such disease is in accordance with the present invention comprises administering interferon at a dosage of 0.01 to about 5 IU/lb* [~19 to ~9570 **units.**/average male American] *per day in a dosage form adapted to promote contact of said dosage of interferon with the oral and pharyngeal mucosa of said animal.* ***Preferably****, the dosage of interferon is from 0.1 to about 4.0 IU/lb* [~191 to ~7660 **units**/average male American] *per day,* ***more preferably*** *0.5 to about 1.5 IU/lb of body weight* [~957 to ~2870 **units**/average male American] *per day.*[1]
>
> [1] *Using the same conversion formula used in the Examiner's Answer (i.e., IU/lb X 1 unit/0.1 IU X 2.2 Kg/lb X 87 Kg average American).*

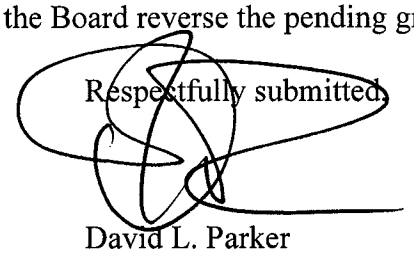
As stated previously, the dose range taught by Cummins '382 is lower than the range recited in the instant claims. Furthermore, Cummins '382 teaches that the preferred dose ranges for treatment of "immuno-resistant disease" are even lower, with the most preferred range being ~ 957 to 2870 units/average American male. In view of these teachings, Applicant maintains that Cummins '382 teaches away from the higher oral dose ranges the instant claims or of Cummins '985 for the treatment of autoimmune diseases such as IDDM.

Cummins '985 on the other hand concerns oral administration of interferon in a range encompassing the claimed range, but teaches the use thereof for treating viral a neoplastic disease. The Examiner has stated that Cummins '985 is relied upon because it teaches an effective dose range of oral interferon in a human. However, as Applicant has previously stated, Cummins '985 concerns doses of oral interferon that may be used to *enhance* a mammalian immune response, an effect contrary to that sought in the treatment IDDM. The Examiner has

rebuffed this point by stating that Cummins '985 discloses that "in addition to use in antiviral and anti-tumor therapy, interferon has rather recently been noted to possess immunomodulatory effects, both immunopotentiating and immunosuppressive in nature" (column 3, lines 33-35). However, merely noting that interferon may have immunosuppressive activity provides no teaching as to what interferon dose range may affect such activity. Thus, Applicant maintains that one of skill in the art would not reasonably expect the oral interferon doses shown to stimulate the immune system by Cummins '985 to be effective in IDDM therapy. In fact, the skilled artisan would be quite unmotivated to use such doses in view of their apparent immunostimulatory effect.

Neither Sobel nor Cummins '382 teach the critical oral dose range of the instant claims necessitating the Examiners reliance on the range from Cummins '985. However, since Cummins '985 teaches oral doses of interferon for the treatment of disease far removed from IDDM the skill artisan would neither be motivated to combine Sobel and Cummins '985 nor expect success in such a combination. Furthermore, the methods of treating autoimmune disease with low-dose interferon taught by Cummins '382 clearly teach away from the higher dose ranges of the instant claims and the Cummins '985 reference. In light of these arguments, it is respectfully submitted that none of the pending claims are properly rejected under 35 U.S.C. §103. Therefore, Appellants request that the Board reverse the pending grounds for rejection.

Respectfully submitted,



David L. Parker
Reg. No. 32,165
Attorney for Appellants

FULBRIGHT & JAWORSKI L.L.P
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3085

Date: September 11, 2006